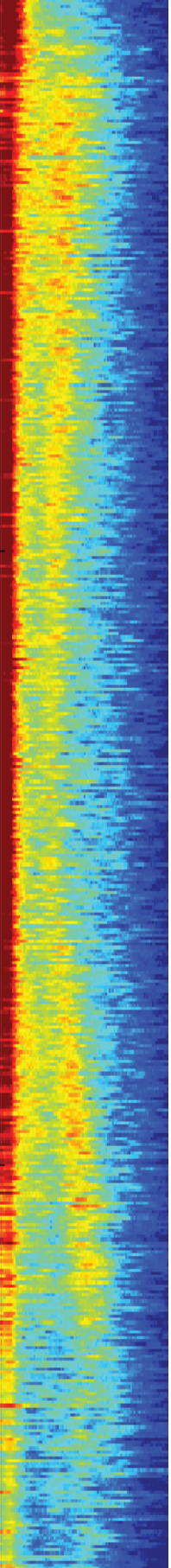
Intravenous drug dose optimization and drug effect monitoring in anaesthesia

Sahinovic, Marko



Bispectral index values and propofol concentrations at loss and return of consciousness in patients with frontal brain tumours and control patients

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Authors
M.M. Sahinovic[1], U Beese[1], E.H. Heeremans[1], A. Klamar[1], K. van Amsterdam[1], R.J.H.M. Steenbakkers[2], H. Kuiper[3], R.Spanjersberg[1], R.J.M. Groen[4], M.M.R.F Struys[1,5], A.R. Absalom[1]

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Abstract

Background. The influence of frontal brain tumours on bispectral index (BIS) measurements and propofol requirements is unknown. The primary aim of our study was to determine whether BIS values recorded at loss and return of consciousness (LOC and ROC, respectively) differ between patients with unilateral frontal brain tumours and control patients. Secondary goals were to compare propofol requirements for LOC and to determine whether there were significant inter-hemispheric differences between BIS values in tumour and control patients.

Methods. We enrolled 20 patients with a frontal brain tumour and 20 control patients. Bilateral BIS measurements were done during induction of propofol anaesthesia, during recovery of consciousness, and during a second induction of anaesthesia. The isolated-forearm test was used to determine the moments of LOC1, ROC, and LOC2. Arterial blood samples were obtained every 4 min for determination of measured propofol concentrations.

Results. The median BIS values recorded at LOC1, ROC, and LOC2 did not differ between the groups. There were no significant inter-hemispheric differences in BIS in tumour and control patients. The median [inter-quartile range (IQR)] total propofol doses at LOC1 were 82 (75–92) and 78 (68–91) mg in tumour and control patients, respectively. The median (IQR) measured plasma propofol concentrations at LOC1 were 12 (9–14) and 13 (11–15) mg ml^{-1} in the tumour and control groups, respectively.

Conclusions. The presence of a frontal brain tumour did not affect ipsilateral BIS values, and so need not influence the placement of unilateral BIS electrodes if BIS monitoring is used to titrate propofol anaesthesia.

Introduction

Many anaesthetists measure and record the bispectral index (BIS) (Bispectral Index, Covidien, Boulder, CO, USA) during craniotomy for excision of brain tumours, and use the BIS to guide titration of the anaesthetic agents. However, there have been few studies investigating the influence of brain tumours on the reliability of the BIS as a measure of hypnosis. As far as we know, no studies have specifically addressed the issue of the influence of frontal brain tumours on the relationship between the BIS and conscious state.

One study, involving 13 patients with small supra- and infra-tentorial tumours, and 13 control patients, was designed to evaluate the relationship between estimated effect-site concentrations and the BIS during loss of consciousness (LOC).[1] For induction of anaesthesia, propofol was administered at a rate of 2000 mg h^{-1} in all patients, but achieved plasma concentrations were not measured. Although the authors found significantly higher overall BIS values over time in tumour patients during the induction, and higher BIS values for estimated effect-site concentrations 2.5 mg ml^{-1}, there were no statistically significant differences in BIS and propofol concentrations at LOC. Overall, the findings were inconclusive, difficult to interpret, and limited by the small sample size and by the inclusion of patients with non-frontal brain tumours.

It is a common perception among anaesthetists that patients with brain tumours are sensitive to the effects of commonly used anaesthetic agents, such as propofol, and accordingly they administer cautious induction doses. This practice, recommended in some textbooks[2], is chiefly supported by clinical experience, expert opinion, and by one small study which did indeed show evidence that propofol requirements are decreased in patients with large supratentorial brain tumours[3]. During neurosurgery, propofol-based total i.v. anaesthesia is commonly practiced, with propofol often administered by target-controlled infusion (TCI). If there are pharmacokinetic, pharmacodynamic, or both differences among patients with tumours, then the models which are used for TCI propofol may be inaccurate in these patients.

Overall, it remains unclear whether anaesthetic dose titration according to the BIS is advisable in patients with cranial tumours, and whether or not these patients are more susceptible to the hypnotic effects of propofol. The primary aim of our prospective observational study was to compare BIS values recorded at LOC and ROC among patients with unilateral frontal brain tumours and patients with no brain tumour. Secondary goals were to determine whether there were differences between BIS values recorded on the ipsilateral and contralateral hemispheres in tumour patients, and to compare propofol dose and measured plasma concentration requirements for LOC in these two patient groups.

Methods

Clinical protocol

After institutional ethics committee approval (UMCG ethics committee number 2009058) and registration at ClinicalTrials.gov (NCT01060631), we obtained informed consent from 53 ASA I–III patients older than 18 yr. of age for inclusion in the study. The study group comprised 24

patients with a known frontal intracranial tumour proven by a recently obtained magnetic resonance imaging (MRI) image, who were undergoing an elective tumour excision. Patients were prospectively assessed for the presence of significant neurological deficits. Those with any sensorimotor or cognitive deficits that may have interfered with assessments of consciousness

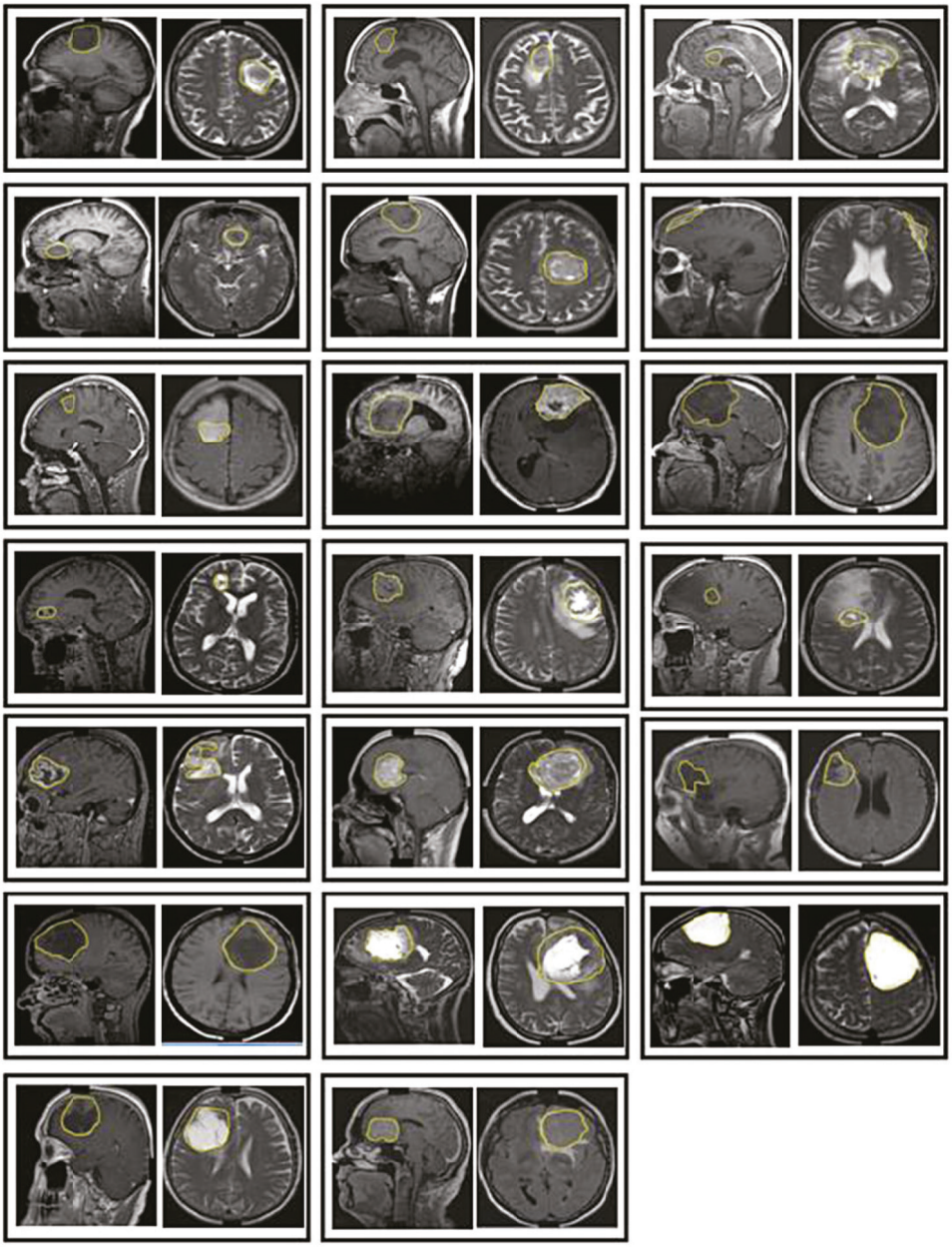

Figure 1. MRI images of tumour patients

were not considered eligible for the study. For MRI images, see Figure 1. The control group comprised 29 patients without intracranial pathology planned to undergo an elective spinal neurosurgical operation. Exclusion criteria for both groups were any conditions or treatments that could potentially interfere with respiratory or cardiovascular status of the patient during the study. Complete group allocation is reported in Figure 2.

The study was performed before any surgical intervention in a quiet operating theatre, with the following personnel present: one coordinating researcher, one anaesthetist responsible for the safety and anaesthetic care of the patient, one anaesthetic nurse, and a second anaesthetist responsible for blood sampling and other tasks.

On arrival in the operating theatre, an i.v. cannula was inserted in the non-dominant hand or forearm. All patients received an i.v. infusion of crystalloid solution, at a rate of 500 ml h^{-1}, to deliver the required drugs and fluids during the study period. After the placement of routine cardiovascular and respiratory monitors, an intra-arterial catheter was inserted under topical anaesthesia in the non-dominant radial artery and connected to a pressure transducer. Bilateral BIS electrodes were placed as recommended by the manufacturer and bilateral BIS and bilateral frontal electroencephalographic activity was recorded using a Vista monitor (Covidien) with seven electrodes. Heart rate, three-lead ECG, capnography, and pulse oximetry and invasive arterial pressure were also recorded continuously using a Philips IntelliVue MP50 (Philips, Eindhoven, The Netherlands) monitor. Numerical and wave-form data were recorded electronically using Rugloop II & software (Demed, Temse, Belgium). The raw electroencephalogram was digitized at a rate of 128 Hz and stored for post hoc analysis.

The timeline of the study is shown in Figure 3. Anaesthesia was induced with continuous i.v. infusion of propofol 2% at a rate of 100 ml h^{-1}. During induction of anaesthesia, patients were verbally prompted every 10 s to squeeze the dominant hand. For the verbal commands, an electronic recording was relayed to the patient by headphones using Microsoft Windows Media Player at maximum volume. The coordinating researcher remained at the patient's dominant side and could hear the auditory commands. The observer informed the other investigators of LOC at the time of the second failure of the patient to respond to the verbal command. The following were then performed as soon as possible: the time of the loss of response was recorded electronically (by free text entry in RUGLOOP) and on paper, the estimated effect-site concentration at LOC1 was noted, the first arterial blood sample was withdrawn and the time of withdrawal of the sample recorded, the fixed rate propofol infusion was stopped, and an effect-site TCI propofol infusion was begun with the target concentration set to that noted at LOC1.

To improve the quality of EEG signals and BIS registration, rocuronium bromide (Fresenius-Kabi, France) was administered and a laryngeal mask airway (LMA) was inserted in order to maintain a patent airway. To facilitate registration of subsequent responses to commands, the isolated forearm technique was applied. Thus, before administration of rocuronium, a padded tourniquet was applied to the dominant upper arm and inflated 20% above the systolic arterial pressure.

At 15 min after LOC1, a noxious stimulus in the form of a 30s electrical tetanic stimulus (100 Hz, 60 mA) was applied to the dominant forearm. At 20 min after LOC, the propofol TCI target was set to zero (thereby stopping the infusion) and patients were again verbally prompted every 10 s to squeeze the dominant hand. The second subsequent purposeful response to this prompt was noted as return of consciousness (ROC), the time was noted, and the propofol infusion was restarted at 100 ml h^{-1} until the response ceased and the patient lost consciousness for the second time (LOC2). This signalled the end of the study and further preparation for surgical procedure was commenced as planned. Propofol infusions were administered by Orchestra DPS infusion pumps (Fresenius-Kabi) controlled by the RUGLOOP II software. In addition to controlling the infusion pumps, RUGLOOP calculated and recorded plasma and effect-site concentrations using the Schnider model[4] during fixed rate propofol administration, and calculated, implemented, and recorded the required propofol infusion rates during TCI administration. RUGLOOP also retrieved and electronically recorded all measured physiological parameters, including BIS values and unprocessed EEG signals, during the study.

Because of the fact that sympathomimetic agents may influence the BIS[5] administration of vasopressors was not permitted. However, if the physician responsible for the clinical care of the patient felt that such an intervention was necessary to maintain the safety of the patient, then in keeping with GCP, such therapy was administered, but the data of the patient were excluded from further analysis, and a replacement patient was eventually enrolled. The latter was also applied to patients in whom there were no clear responses to command, despite other clear signs of consciousness. Replacement was approved by the ethical committee.

Arterial blood samples (10 ml) were drawn every 4 min throughout the study, starting at the moment of LOC1, with additional samples at ROC and at LOC2. These blood samples were kept refrigerated until arrival at the laboratory where they were centrifuged, and the supernatant was removed. The resulting plasma samples were stored at -220 ^{O}C. After thawing, propofol assays were performed at room temperature within 24 h as described below. This propofol assay is based upon an assay for propofol in cerebrospinal fluid as described by Peeters and colleagues[6].

Plasma propofol concentration measurement

Extraction procedure

Fifty microlitres of thymol stock solution (20 mg litre21) were added to 200 ml of plasma samples. Two hundred microlitres of water, 400 ml of borate buffer (pH¼9), and 500 ml of n-heptane were added and mixed thoroughly for 20 min on a Heidolph Reax 2 mixer (Scientific Ltd, New Brunswick, NJ, USA). After centrifugation for 5 min at 3000 rpm, the glass tube was placed at 2408C. The organic layer was then transferred to an injection vial and 1.0 ml was injected to the GC-MS system.

Apparatus and chromatographic conditions

A PerkinElmer Autosystem XL GC-MS system (Benelux BV) with a PerkinElmer automatic sampler and a PerkinElmer Turbo-mass Gold, Quadrupole detector was used. Separation was performed by injection in the spitless mode (valve time 50 s) of 1.0 ml of the extract to a Chrompack VF 5 ms MS capillary column (25 × 0.25 mm ID, film thickness 0.25mm, Agilent, art.CP8941).The injector temperature was 250 ^{O}C and the oven temperature was held at 80 ^{O}C for 1 min, increased at 10OC min-1 upto160 ^{O}C. The transfer line temperature was set to 250 ^{O}C. The helium gas flow rate was 1.5ml min^{-1}.The electron energy was set at 70eV. The propofol and thymol ions were detected by using molecular ions at m/z 178 and 150, respectively, and for the quantitation of the major ions due to loss of methyl groups at m/z 163 and 135, respectively. Under these conditions, the retention times of propofol and thymol were 6.54 and 5.71 min, respectively.

Accuracy and precision

The calibration curve was linear (weighing 1/x) in the range 0.25–25 mg litre^{-1}. The limit of quantitation was defined as the concentration where the overall bias and coefficient of variation (CV) of the accuracy and precision lies within 20% and proved to be 0.252 mg litre^{-1}. Intra-and interday CVs (%CV) were obtained using plasma samples spiked with four known quality control (QC) concentrations of propofol (0.252, 0.804, 10, and 20.1 mg litre-1). For 3 days, the QC was prepared and analysed in six-fold. Propofol plasma concentration in control samples was stable at temperatures between 4 and 20OC for at least 4 days and during four freeze/thaw cycles. Results are shown in the Appendix.

Tumour volume measurement

Preoperative MRI scans of all tumour patients were uploaded to a radiotherapy treatment planning system Pinnacle 9.1 & (Philips). Under the supervision of a dedicated head and neck radiation oncologist (R.J.H.M.S.), the tumour boundaries were manually drawn on transverse slices of either T1 (with or without gadolinium enhancement) or T2 MRI images. Using these contours, Pinnacle software was then used to calculate tumour volumes.

Statistical analysis

Our sample size calculation was based on the following parameters and assumptions. We chose α of 0.05, β of 0.2, and a clinically significant difference in the mean BIS value at LOC and ROC of 10. Based on an assumption that the variability in BIS at LOC would be similar to that in a previously reported study [where the standard deviation (SD) was 11 and 20 in control and tumour patients, respectively][1], we calculated that two groups of 18 patients needed to be included in the study, and arbitrarily rounded this up to 20 per group. We tested for normality the distribution of all samples (LOC1, ROC, and LOC2) for both groups for all reported variables, using the Shapiro–Wilk test. We accepted the hypothesis of normal distribution if P=0.05. Patient characteristic variables were normally distributed. Differences in patient characteristic variables were tested for statistical significance with Student's t-test for continuous variables and the x2 test for categorical variables. BIS, propofol concentrations, and haemodynamic variables were generally all normally distributed at most sampling points. However, for each variable, the distribution was not normal

in one group (tumour or control group) at at least one sampling point. Therefore, these variables are summarized as the median [inter-quartile range (IQR)]. Differences in these values between the groups were tested for statistical significance with the Mann–Whitney U-test or Student's t-test as appropriate.

Results

The CONSORT diagram summarizing eligibility and enrolment is shown in Figure 2. A total of 53 patients consented to enrolment in the study. One consented patient in each group did not participate in the study because of inadequate staffing on the day of the procedure. In one patient, the study was terminated soon after the start when unexpected (patient) movement dislodged the arterial cannula. Three patients in the study group and five patients in the control group were excluded from further analysis, because they did not show clear responses to command during induction or recovery, despite other signs of consciousness (such as purposeful movement). One further patient was excluded from the analysis in the control group because of hypotension requiring administration of vasopressors.

Patient characteristic data and tumour characteristics of the remaining patients are displayed in Tables 1 and 2. The mean (SD) tumour volume was 59.5 (43.6) cm^3. Among the tumour patients, 10 were receiving anti-epileptic medication and 17 were receiving steroids before operation; among the control patients, none were using anti-epileptic medication or steroids. There were no significant differences in patient characteristics between the study and control groups.

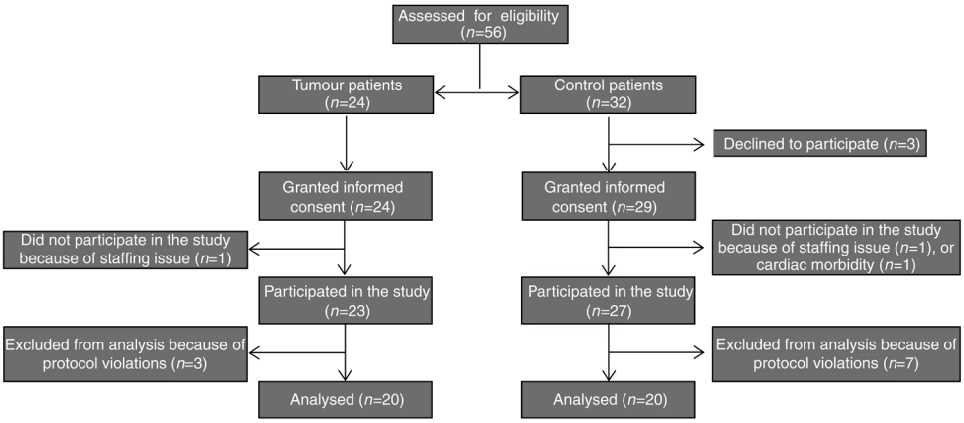

Figure 2. Consort diagram describing the flow of subjects with the study

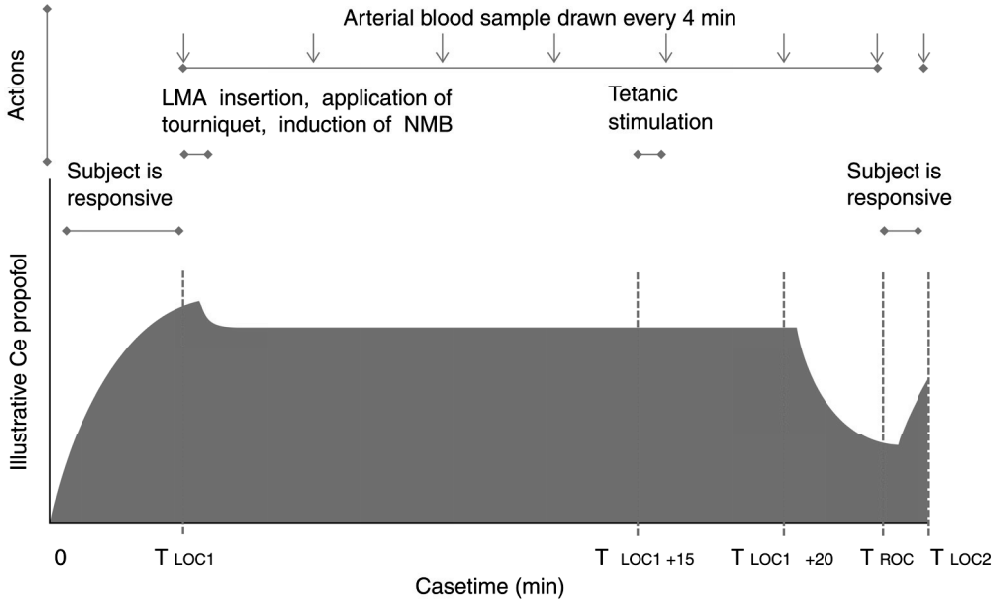

Figure 3. Study protocol graphically showing the order of events during the data acquisition

BIS values for all patients before and after each LOC1, ROC, and LOC2 are shown in Figure 4. The median BIS values recorded at these transitions did not differ between the groups (Fig. 5), and were not different between hemispheres in both tumour and control patients. Six patients in the study group and five patients in the control group showed purposeful movements of the unparalysed arm in response to the noxious stimulus 15 min after LOC1.

	Tumour patients	**Control patients**	***P*-value**
Age (yr)	50 (14)	56 (10)	0.16
Gender (M/F)	12/8	9/11	0.31
Height (cm)	177 (10)	174 (8)	0.93
Weight (kg)	84 (13)	79 (14)	0.30
ASA (I/II/III)	2/15/3	8/12/0	0.23

Table 1. Patient characteristics. Mean (SD)

	Frontal
Tumour location	
Side L/R	12/8
Tumour pathology (*n*)	20
Glioma [*n* (%)]	8 (40)
Meningioma [*n* (%)]	8 (40)
Metastasis [*n* (%)]	4 (20)
Tumour dimensions [mean (SD)]	
Anterior/posterior (cm)	5.1 (1.9)
Lateral/medial (cm)	4.1 (1.8)
Coronal/caudal (cm)	4.4 (1.7)
Volume (cm^3)	59.5 (43.6)
Midline shift (Y/N)	15/5
Oedema (Y/N)	16/4

Table 2. Tumour characteristics

LOC1 occurred equally fast in both groups [tumour patients 148 s (24) vs control patients 145 s (38)].The median (IQR) total propofol doses at LOC1 were 82 (75–92) and 78 (68–91) mg in patients with and without brain tumours, respectively.

There were neither differences in estimated and measured plasma propofol concentrations nor in estimated effect-site concentrations, at any of the transitions of consciousness (Table3). ROC occurred on average 17.3 (5.5) min after interruption of propofol infusion in tumour patients and 7.5 (5.3) min in control patients.

Discussion

Frontal brain tumours might reasonably be expected to contain tissue that is electrically pathologically active or that is at the very least not interacting normally with adjacent neurones. Thus, the presence of a tumour, or of cerebral oedema, in the vicinity of an EEG electrode might result in recorded electrical activity that is different from that found on the contralateral side. Likewise, it may also result in recorded activity that has different morphology, frequency, or phase content for a given state of consciousness, when compared with other patients. Since the BIS calculation depends on all of these factors[7], we used a bilateral BIS recording montage and monitor to investigate whether the presence of a unilateral frontal brain tumour has an influence on measured BIS values recorded at transitions between consciousness and unconsciousness. In patients with tumours, we found no significant differences between BIS values recorded over the ipsilateral and contralateral hemispheres at these transitions. Furthermore, there were no significant differences among the BIS values recorded at the moments of transition of conscious state among tumour and non-tumour (control) patients.

These findings are consistent with those of Ferreira and colleagues[1] who reported that even though BIS values were higher in patients with brain tumours during induction, the BIS values at the moment of LOC did not significantly differ between both groups. The development of the BIS algorithm and monitor has been described in detail[7]. In essence, the algorithm monitor was developed by discriminant analysis of a range of candidate mathematical and statistical

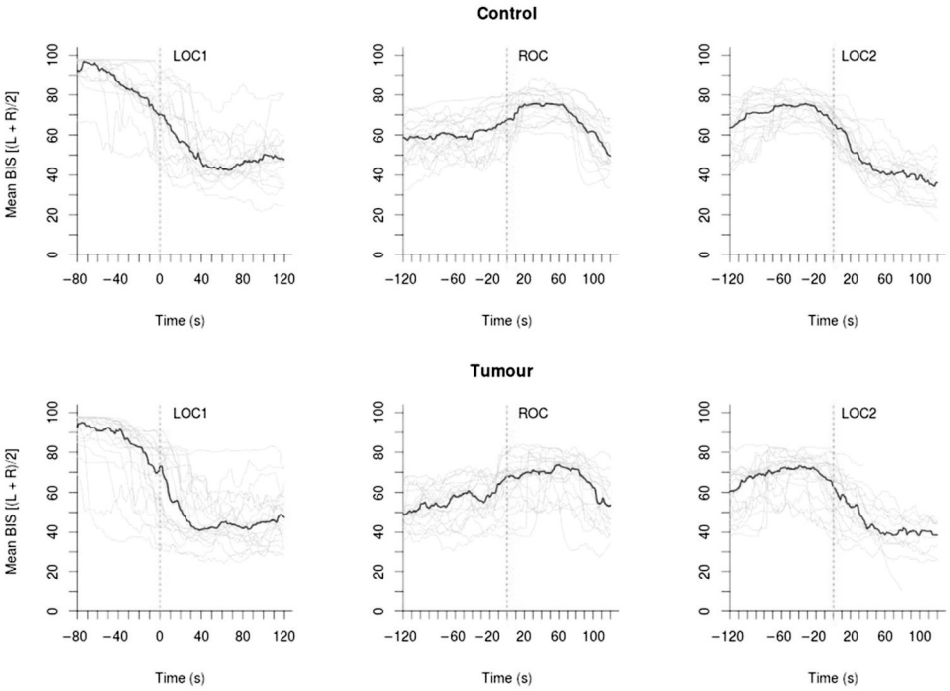

Figure 4. Plots representing individual (thin line) and average (thick lines) BIS values [(BIS value collected over the left hemisphere + BIS value collected over the right hemisphere)/2] of patients recorded around the time of LOC or ROC for control and tumour patients. Time 0 is the moment of transition of consciousness. LOC1, the first moment of loss of consciousness. LOC2, the second moment of loss of consciousness. ROC, the moment of return of consciousness.

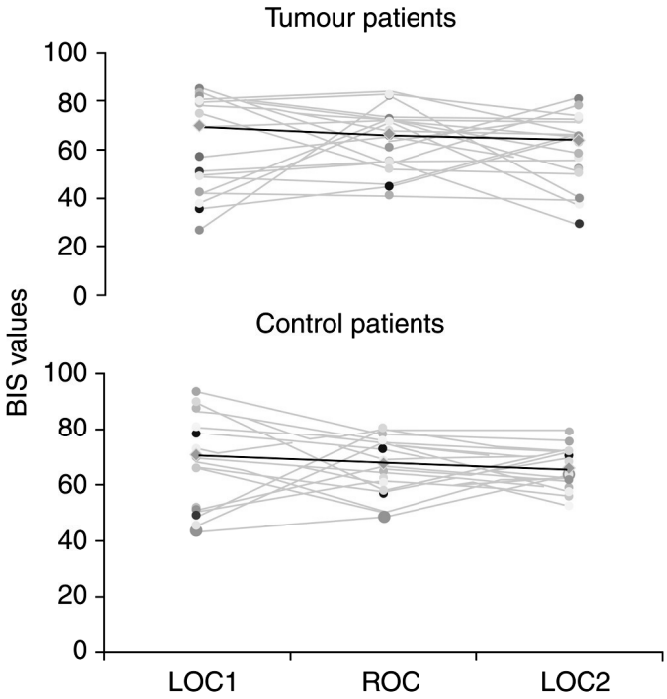

Figure 5. Plots representing individual (thin lines) and median (thick lines) BIS value collected over the left hemisphere + BIS value collected over the right hemisphere)/2] of patients recorded around the time of LOC or ROC for control and tumour patients. Time 0 is the moment of transition of consciousness. LOC1, the first moment of loss of consciousness. LOC2, the second moment of loss of consciousness. ROC, the moment of return of consciousness.

parameters calculated from the EEG of normal volunteers, to provide an index of the depth of hypnosis. The BIS is sensitive to some sources of interference (e.g. signals from the electromyogram can cause false elevations)[8], and can detect some, presumably subtle, changes such as a change in electrical activity when ketamine is used as an anaesthetic adjunct.[9] However, some studies have shown the BIS monitor output to be insensitive to significant changes in raw EEG. In one study, no differences were found in BIS values measured over the left and right hemisphere in patients undergoing the Wadatest[10]. During this test, one hemisphere is rendered functionally inactive by intra-carotid injection of a short-acting barbiturate. In this study, despite the fact that the unprocessed EEG showed a significant lateralized cortical effect, there was no difference between left and right BIS values. All-in- all, with regard to our patients, two possibilities exist. The first is that the presence of frontal brain tumours in our patients did not result in cortical EEG changes. The second possibility is that changes were induced, but were not detected by the BIS monitor. To determine which of these was the case, further studies, for which comprehensive multichannel EEG recording, would be required.

	Control patients	Tumour patients
LOC 1		
Cp estimated	14.6 (13.4–15.2)	14 (13.4–14.6)
Cp measured	12.6 (11.5–15.1)	11.5 (9.2–14.4)
Ce estimated	6.4 (5.2–7.8)	6.1 (5.4–6.6)
ROC		
Cp estimated	0.9 (0.7–1.2)	0.9 (0.8–1.1)
Cp measured	0.8 (0.6–1.1)	0.7 (0.5–0.8)
Ce estimated	1.1 (0.8–1.4)	1.0 (0.7–1.3)
LOC 2		
Cp estimated	12.5 (11.8–14.2)	12.3 (11.1–14.0)
Cp measured	13.4 (11.1–15.4)	10.4 (8.7–13.9)
Ce estimated	4.0 (3.5–5.1)	4.1 (3.3–4.9)

Table 3. Median (Q1-Q3) estimated propofol concentrations at transitions of consciousness. Cp, propofol plasma concentration. Ce, propofol effect-site concentration

A secondary aim of our study was to investigate whether propofol requirements were different in patients with frontal brain tumours. There are many potential reasons why the presence of a brain tumour might alter the pharmacodynamics of a hypnotic agent. These include the presence of local pressure effects on pathways and structures important for consciousness (e.g. brainstem and thalamus), chemical irritation, inflammation, and the adverse effects of raised intracranial pressure on cerebral blood flow. Previous work by Chan and colleagues[3] had suggested that propofol doses required to suppress responses to verbal and tetanic stimuli are lower in patients with large brain tumours [mean (SD) 69.6 (27.1) cm^3] compared with control patients and patients with smaller tumours [mean (SD) 5 (4.8) cm^3]. We could not confirm these findings. In our study, tumour and control patients showed neither differences in propofol dose required for LOC nor differences in measured plasma propofol concentration and estimated effect-site concentration at transitions of consciousness. The reasons for this discrepancy are not clear, but may be related to factors such as tumour size and position. The average tumour volume among our patients was 58 (43) cm^3 and thus smaller than the volume of large tumours in Chan and colleagues' study.[3] Our study was conducted exclusively in patients with frontal brain tumours, whereas Chan and colleagues[3] included patients with cerebral tumours in a variety of locations.

There are a few limitations of our study. As with most BIS data sets recorded at transitions of consciousness, the variability in BIS values is high, especially at the moment of LOC before neuromuscular blocking agent administration (Fig. 4). The processing delay of the BIS monitor varies with the signal quality. During LOC, the EEG signal quality is often poor since it is contaminated with signals from the muscles, thereby causing variable processing delays, and greater variability in BIS values. A second limitation is the unavoidable inherent imprecision in registration of the

moment of LOC or ROC. During transitions of consciousness, the BIS often changes rapidly. Thus, any delays in detecting the moment of LOC or ROC will lead to inaccurate registration of the BIS at the transition and increase the variability in the data. During the planning of the study, we sought a balance between precise determination of the moment of LOC/ROC and alteration of the level of consciousness by patient stimulation. The 10 s interval we chose for assessment of the state of consciousness thus limits the precision of the data.

Finally, it should be remembered that the BIS was designed to provide an index or estimate of the hypnotic component of anaesthesia. While it may be said that the monitor output provides some idea of the probability of consciousness or recall, it is not designed to detect the moment of LOC, or to give an absolute indication of the presence or absence of consciousness. In this way, the monitor output is analogous to that of an arterial pressure monitor, which reports the arterial pressure, but makes no judgement on the presence or absence of hypotension, or ischaemia.

In conclusion, BIS values at LOC and ROC are similar in patients with frontal brain tumours, to those recorded in control patients. Propofol requirements for LOC were also similar among tumour and non-tumour patients. The presence of a frontal brain tumour need not influence the placement of unilateral BIS electrodes, nor the decision whether or not to use BIS monitoring for titrating anaesthetic administration.

Declaration of interest
M.M.R.F.S. and A.R.A. are both editors of the British Journal of Anaesthesia but were not involved in the editorial handling of this manuscript.

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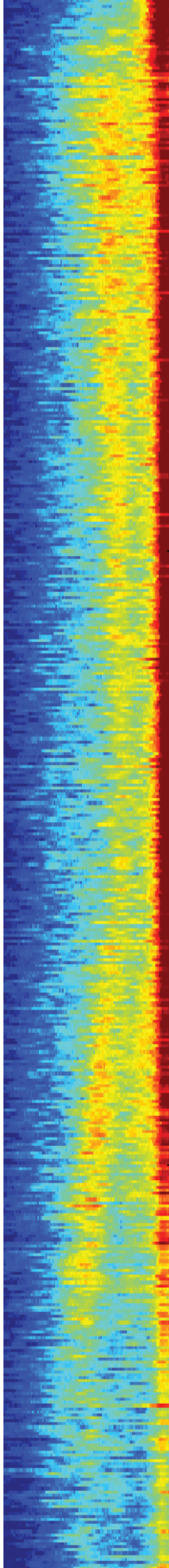

Affiliation at the time of publication
[1]Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands

[2]Primate Research Institute, Kyoto University, Inuyama, Aichi, Japan

[3]Department of Anaesthesia, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium